

FOOD AND DRUG ADMINISTRATION

Center for Tobacco Products (CTP)

Tobacco Product Constituents Subcommittee

of the

Tobacco Products Scientific Advisory Committee (TPSAC)

Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, MD

June 8-9, 2010

These summary minutes for June 8-9, 2010 meeting of the Tobacco Product Constituents Subcommittee of the Tobacco Products Scientific Advisory Committee of the Food and Drug Administration were approved on __8/17/10__.

I certify that I attended the June 8-9, 2010 meeting of the Tobacco Product Constituents Subcommittee of the Tobacco Products Scientific Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

____---S---____
Karen M. Templeton-Somers, Ph.D.
Acting Designated Federal Official

____---S---____
Dorothy Hatsukami, Ph.D.
Chair, Tobacco Product Constituents Subcommittee

The Tobacco Product Constituents Subcommittee of the Tobacco Products Scientific Advisory Committee of the Food and Drug Administration, Center for Tobacco Products met on June 8-9, 2010 at the Holiday Inn, The Ballrooms, Two Montgomery Village Avenue, Gaithersburg, MD. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the submissions from the public. The meeting was called to order by Dorothy Hatsukami, Ph.D. (Subcommittee Chair); the conflict of interest statement was read into the record by Karen M. Templeton-Somers, Ph.D. (Acting Designated Federal Official). There were approximately 120 persons in attendance. There were 5 presentations in the Open Public Hearing session.

Proposed Agenda: The subcommittee will receive presentations and discuss the development of a list of harmful or potentially harmful constituents, including smoke constituents, in tobacco products. Topics for discussion will include the criteria for selection of the constituents, developing a proposed list of harmful or potentially harmful constituents, the rationale for including each constituent, and the acceptable analytical methods for assessing the quantity of each constituent. A second meeting of this subcommittee, to continue these discussions as necessary, and to include ancillary and normalization standards for the constituents, will be scheduled for the summer of 2010.

Attendance:

Tobacco Products Scientific Advisory Committee Members Present (Voting):

TPSAC Members (*voting*): Dorothy K. Hatsukami, Ph.D. (Chair), Jack E. Henningfield, Ph.D.

TPSAC Members (*non-voting Industry Representatives*): Jonathan Daniel Heck, Ph.D., DABT (Representative of the tobacco manufacturing industry); John H. Lauterbach, Ph.D., DABT (Representative for the interest of small business tobacco manufacturing industry)

Consultants (*non-voting*): David Burns, M.D., Mirjana Djordjevic, Ph.D., William A. Farone, Ph.D., Stephen S. Hecht, Ph.D., Jennifer Jinot, Richard O'Connor, Ph.D., Clifford Watson, Ph.D.

FDA Participants at the table (*non-voting*): David L. Ashley, Ph.D., Corinne G. Husten, M.D., M.P.H.

Designated Federal Official (*Acting*): Karen M. Templeton-Somers, Ph.D.

Open Public Hearing Participants:

Ryan Lanier & Curtis Wright
Ronald Tully
Mark Haney
Richard G. Higby, Ph.D.
Kerry Lane, MD

The Agenda proceeded as follows:

June 8, 2010

Call to Order

Dorothy Hatsukami, Ph.D.
Chair, Tobacco Product Constituents
Subcommittee

Conflict of Interest Statement

Karen M. Templeton-Somers, Ph.D.
Acting Designated Federal Official, FDA

Introduction of Subcommittee Participants

Charge to the Group: Harmful and Potentially
Harmful Tobacco Product Constituents

Corinne Husten, M.D., M.P.H.
CTP

Examples of Lists of Harmful/Potentially
Harmful Constituents and the Rationale for Inclusion

Patricia Richter, Ph.D.
Office on Smoking and Health
National Center for Chronic Disease
Prevention and Health Promotion
Centers for Disease Control and Prevention

Industry Presentations: Preliminary Information Concerning the Establishment of a List of Harmful
and
Potentially Harmful Tobacco Product Constituents

Michael W. Ogden, Ph.D.
R. J. Reynolds Tobacco Company
(On behalf of multiple tobacco product
manufacturers)

David Michael Johnson, Ph.D.
Council of Independent Tobacco
Manufacturers of America (CITMA)

Carcinogen Classification Criteria

Patricia Richter, Ph.D.

Subcommittee Discussion of Criteria for Determining Initial List of Harmful/Potentially
Harmful Constituents

Open Public Hearing

Proposed Methodology Options for Analysis
of Constituents

Clifford O. Watson, Ph.D.
National Center for Environmental Health
Centers for Disease Control and Prevention

Subcommittee Discussion and Development of List of Harmful/Potentially Harmful Constituents

June 9, 2010

Call to Order

Dorothy Hatsukami, Ph.D.
Chair, Tobacco Product Constituents
Subcommittee

Conflict of Interest Statement

Karen M. Templeton-Somers, Ph.D.
Acting Designated Federal Official, FDA

Subcommittee discussion on list of harmful/potentially harmful constituents, rationale, and proposed methodology

Methodologies used to Develop Toxicology Summaries

Patricia Richter, Ph.D.
Office on Smoking and Health
National Center for Chronic Disease
Prevention and Health Promotion
Centers for Disease Control and Prevention

Subcommittee discussion and development of harmful/potentially harmful constituents, rationale, and proposed methodology

Finalize draft list of harmful and potentially harmful constituents

Subcommittee discussion of the Questions to the Subcommittee

Adjourn

~~~~~  
***Questions to the Subcommittee:***

1. What criteria do you recommend to TPSAC for selecting the H/PH constituents in tobacco products or tobacco smoke (which will be used in developing the initial list)?
2. What H/PH constituents do you recommend to TPSAC be included on the initial FDA list and how do they meet the criteria?
3. What established analytical methods do you recommend to TPSAC for assessing the quantity of each H/PH constituent in tobacco products or tobacco smoke?

*Questions 1, 2 and 3 were addressed concurrently. The Subcommittee reviewed the example lists in the "Summary Table of Example Government or WHO Lists", and the information contained in "Example Constituents and their Potential Association with Selected Tobacco-Related Diseases". (Both of these documents were provided in the background materials.) The Subcommittee included on the initial list all constituents that were potentially associated with the tobacco-related diseases of cancer, respiratory and cardiovascular disease, and addiction. The list produced by the end of the meeting is attached.*

3. What scientific parameters need to be considered in choosing methods to be used?

*The Subcommittee discussion centered on defining acceptable analytic methods, and recommended that experiences in other areas be evaluated, such as the acceptable criteria for variability in EPA measurement, as well as other Centers in FDA, such as foods.*

*Initially, FDA could adopt processes used by other organizations and countries. The variability of products in the US market will only be known after it has been measured. Variability can come from a number of sources, including the variability of the method, the reliability of the method, reproducibility and inter-laboratory variability.*

*Care should be taken to be sure that similar bases are used for making comparisons.*

5. What are your scientific recommendations on:

- Sampling, based on information about variability of products?

*There is no baseline information on the products in the US, so the Subcommittee felt that several measurements, at different intervals, would be needed to see how much variability is present, before definitive recommendations could be made on sampling intervals. It may be possible to get data from Canada to get an estimate of the variability within brands over time.*

- Smoking regimens?

*The amount of smoke measured changes with the regimen, as does the ranking of the constituents measured, providing another source of variability. At least two smoking regimens are needed. The Subcommittee recommended starting with the ISO and the Canadian Intense methods, as the most internationally validated, and because there is enough data on these methods that reproducibility can be gauged.*

*The Subcommittee recommends that, for smokeless tobacco products, the Agency should compare methods used internationally, and that 2 methods should also be used for smokeless tobacco products. Guidance is needed for determining a method that would give information on the exposure for 80-90% of the consumers.*

6. What are your scientific recommendations on how values should be normalized:

- By product unit (per can or stick)?
- By volume (smoke volume, gram of smokeless)?
- By nicotine or tar content?

*The Subcommittee felt that all measurements can be relevant, but that it is important that the values are measured on per unit of “something” (can, stick, gram of smokeless, smoke volume, etc.) and how many of these units make up a standard portion. The values can then be converted as needed. Although the manufacturer should determine the “unit dose”, it was recommended that the experience with over-the-counter drugs be considered – “actual use” vs. labeled dose, along with consumer education to understand the information on the label.*

The meeting adjourned at 2:30 p.m. on June 9, 2010.

**Please see the *verbatim* transcript for details of the discussion.**

## Draft Proposed Initial List of Harmful/Potentially Harmful Constituents in Tobacco Products, including Tobacco Smoke

|                    | <b>H/PH<br/>Inhaled from<br/>Smoke</b> | <b>H/PH<br/>Absorbed or<br/>consumed<br/>from tobacco<br/>products</b> | <b>Analytic<br/>Method<br/>Available</b> |
|--------------------|----------------------------------------|------------------------------------------------------------------------|------------------------------------------|
| Acetaldehyde       | YES                                    | YES                                                                    | YES                                      |
| Acetamide          | YES                                    |                                                                        | YES                                      |
| Acetone            | YES                                    |                                                                        | YES                                      |
| Acrolein           | YES                                    |                                                                        | YES                                      |
| Acrylamide         | YES                                    |                                                                        | YES                                      |
| Acrylonitrile      | YES                                    |                                                                        | YES                                      |
| Aflatoxin B-1      |                                        | YES                                                                    | ?                                        |
| 4-Aminobiphenyl    | YES                                    |                                                                        | YES                                      |
| 1-Aminonaphthalene | YES                                    |                                                                        | YES                                      |
| 2-Aminonaphthalene | YES                                    |                                                                        | YES                                      |
| Ammonia            | YES                                    |                                                                        | YES                                      |
| Ammonium Salts     |                                        | Defer                                                                  | YES                                      |
| Anabasine          |                                        | Defer                                                                  | YES                                      |
| Anatabine          |                                        | Defer                                                                  | YES                                      |

|                      | <b>H/PH<br/>Inhaled from<br/>Smoke</b> | <b>H/PH<br/>Absorbed or<br/>consumed<br/>from tobacco<br/>products</b> | <b>Analytic<br/>Method<br/>Available</b> |
|----------------------|----------------------------------------|------------------------------------------------------------------------|------------------------------------------|
| 0-Anisidine          | YES                                    |                                                                        | YES                                      |
| Arsenic              | YES                                    | YES                                                                    | YES                                      |
| A- $\alpha$ -C       | YES                                    |                                                                        | YES                                      |
| Benz[a]anthracene    | YES                                    | YES                                                                    | YES                                      |
| Benz[b]fluoroanthene | YES                                    | YES                                                                    | YES                                      |
| Benz[j]aceanthrylene | YES                                    |                                                                        | YES                                      |
| Benz[k]fluoroanthene | YES                                    | YES                                                                    | YES                                      |
| Benzene              | YES                                    |                                                                        | YES                                      |
| Benzo(b)furan        | YES                                    |                                                                        | ?                                        |
| Benzo[a]pyrene       | YES                                    | YES                                                                    | YES                                      |
| Benzo[c]phenanthrene | YES                                    |                                                                        | YES                                      |
| Beryllium            | YES                                    | YES                                                                    | YES                                      |
| 1,3-Butadiene        | YES                                    |                                                                        | YES                                      |
| Butyraldehyde        | YES                                    |                                                                        | YES                                      |
| Cadmium              | YES                                    | YES                                                                    | YES                                      |
| Caffeic acid         | YES                                    |                                                                        | YES                                      |
| Carbon monoxide      | YES                                    |                                                                        | YES                                      |

|                                         | <b>H/PH<br/>Inhaled from<br/>Smoke</b> | <b>H/PH<br/>Absorbed or<br/>consumed<br/>from tobacco<br/>products</b> | <b>Analytic<br/>Method<br/>Available</b> |
|-----------------------------------------|----------------------------------------|------------------------------------------------------------------------|------------------------------------------|
| Catechol                                | YES                                    |                                                                        | YES                                      |
| Chlorinated dioxins/furans              | YES                                    |                                                                        | YES                                      |
| Chromium                                | YES                                    | YES                                                                    | YES                                      |
| Chrysene                                | YES                                    | YES                                                                    | YES                                      |
| Cobalt                                  | YES                                    |                                                                        | YES                                      |
| Coumarin <i>banned for use in foods</i> |                                        | YES (Group 3)                                                          | YES                                      |
| Cresols                                 | YES                                    |                                                                        | YES                                      |
| Crotonaldehyde                          | YES                                    | YES (Group 3)                                                          | YES                                      |
| Cyclopenta[c,d]pyrene                   | YES                                    |                                                                        | YES                                      |
| Dibenz(a,h)acridine                     | YES                                    |                                                                        | ?                                        |
| Dibenz(a,j)acridine                     | YES                                    |                                                                        | ?                                        |
| Dibenz[a,h]anthracene                   | YES                                    | YES                                                                    | YES                                      |
| Dibenzo(c,g)carbazole                   | YES                                    |                                                                        | ?                                        |
| Dibenzo[a,e]pyrene                      | YES                                    |                                                                        | YES                                      |
| Dibenzo[a,h]pyrene                      | YES                                    |                                                                        | YES                                      |
| Dibenzo[a,i]pyrene                      | YES                                    |                                                                        | YES                                      |
| Dibenzo[a,l]pyrene                      | YES                                    |                                                                        | YES                                      |



|                            | <b>H/PH<br/>Inhaled from<br/>Smoke</b> | <b>H/PH<br/>Absorbed or<br/>consumed<br/>from tobacco<br/>products</b> | <b>Analytic<br/>Method<br/>Available</b> |
|----------------------------|----------------------------------------|------------------------------------------------------------------------|------------------------------------------|
| 2,6-Dimethylaniline        | YES                                    |                                                                        | YES                                      |
| Ethyl Carbamate (urethane) | YES                                    | YES                                                                    | ?                                        |
| Ethylbenzene               | YES                                    |                                                                        | YES                                      |
| Ethylene oxide             | YES                                    |                                                                        | ?                                        |
| Eugenol                    | YES                                    | Defer                                                                  | YES                                      |
| Formaldehyde               | YES                                    | YES                                                                    | YES                                      |
| Furan                      | YES                                    |                                                                        | YES                                      |
| Glu-P-1                    | YES                                    |                                                                        | YES                                      |
| Glu-P-2                    | YES                                    |                                                                        | YES                                      |
| Hydrazine                  | YES                                    |                                                                        | ?                                        |
| Hydrogen cyanide           | YES                                    |                                                                        | YES                                      |
| Hydroquinone               | YES                                    |                                                                        | YES                                      |
| Indeno[1,2,3-cd]pyrene     | YES                                    | YES                                                                    | YES                                      |
| IQ                         | YES                                    |                                                                        | YES                                      |
| Isoprene                   | YES                                    |                                                                        | YES                                      |
| Lead                       | YES                                    | YES                                                                    | YES                                      |
| MeA- $\alpha$ -C           | YES                                    |                                                                        | YES                                      |

|                                                      | <b>H/PH<br/>Inhaled from<br/>Smoke</b> | <b>H/PH<br/>Absorbed or<br/>consumed<br/>from tobacco<br/>products</b> | <b>Analytic<br/>Method<br/>Available</b> |
|------------------------------------------------------|----------------------------------------|------------------------------------------------------------------------|------------------------------------------|
| Mercury                                              |                                        | YES                                                                    | YES                                      |
| Methyl ethyl ketone                                  | YES                                    |                                                                        | YES                                      |
| 5-Methylchrysene                                     | YES                                    |                                                                        | YES                                      |
| 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) | YES                                    | YES                                                                    | YES                                      |
| 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) | YES                                    | YES                                                                    | YES                                      |
| Naphthalene                                          | YES                                    | YES                                                                    | YES                                      |
| Nickel                                               | YES                                    | YES                                                                    | YES                                      |
| Nicotine                                             | YES                                    | YES                                                                    | YES                                      |
| Nitrate                                              | YES                                    | YES                                                                    | YES                                      |
| Nitric oxide/nitrogen oxides                         | YES                                    |                                                                        | YES                                      |
| Nitrite                                              |                                        | YES                                                                    | YES                                      |
| Nitrobenzene                                         | YES                                    |                                                                        | YES                                      |
| Nitromethane                                         | YES                                    |                                                                        | ?                                        |
| 2-Nitropropane                                       | YES                                    |                                                                        | ?                                        |
| N-nitrosoanabasine (NAB)                             | YES                                    | YES (Group 3)                                                          | YES                                      |

|                                 | <b>H/PH<br/>Inhaled from<br/>Smoke</b> | <b>H/PH<br/>Absorbed or<br/>consumed<br/>from tobacco<br/>products</b> | <b>Analytic<br/>Method<br/>Available</b> |
|---------------------------------|----------------------------------------|------------------------------------------------------------------------|------------------------------------------|
| N-Nitrosodiethanolamine (NDELA) | YES                                    | YES                                                                    | YES                                      |
| N-Nitrosodiethylamine           | YES                                    |                                                                        | YES                                      |
| N-nitrosodimethylamine (NDMA)   | YES                                    | YES                                                                    | YES                                      |
| N-Nitrosoethylmethylaniline     | YES                                    |                                                                        | YES                                      |
| N-nitrosomorpholine (NMOR)      |                                        | YES                                                                    | YES                                      |
| N-nitrosornicotine (NNN)        | YES                                    | YES                                                                    | YES                                      |
| N-Nitrosopiperidine (NPIP)      | YES                                    | YES                                                                    | YES                                      |
| N-nitrosopyrrolidine (NPYR)     | YES                                    | YES                                                                    | YES                                      |
| N-nitrososarcosine (NSAR)       |                                        | YES                                                                    | YES                                      |
| Phenol                          | YES                                    |                                                                        | YES                                      |
| PhIP                            | YES                                    |                                                                        | YES                                      |
| Polonium-210 (Radio-isotope)    | YES                                    | YES                                                                    | YES                                      |
| Propionaldehyde                 | YES                                    |                                                                        | YES                                      |
| Propylene oxide                 | YES                                    |                                                                        | YES                                      |
| Pyridine                        | YES                                    |                                                                        | YES                                      |
| Quinoline                       | YES                                    |                                                                        | YES                                      |
| Resorcinol                      | YES                                    |                                                                        | YES                                      |

|                             | <b>H/PH<br/>Inhaled from<br/>Smoke</b> | <b>H/PH<br/>Absorbed or<br/>consumed<br/>from tobacco<br/>products</b> | <b>Analytic<br/>Method<br/>Available</b> |
|-----------------------------|----------------------------------------|------------------------------------------------------------------------|------------------------------------------|
| Selenium                    | YES                                    | YES                                                                    | YES                                      |
| Styrene                     | YES                                    |                                                                        | YES                                      |
| Tar                         | YES                                    |                                                                        | YES                                      |
| 2-Toluidine                 | YES                                    |                                                                        | YES                                      |
| Toluene                     | YES                                    |                                                                        | YES                                      |
| Trp-P-1                     | YES                                    |                                                                        | YES                                      |
| Trp-P-2                     | YES                                    |                                                                        | YES                                      |
| Uranium-235 (Radio-isotope) |                                        | YES                                                                    | YES                                      |
| Uranium-238 (Radio-isotope) |                                        | YES                                                                    | YES                                      |
| Vinyl Acetate               | YES                                    |                                                                        | YES                                      |
| Vinyl Chloride              | YES                                    |                                                                        | YES                                      |

Note: Anabasine, anatabine, myosmine, nornicotine will be discussed at next meeting after NIDA presentation

Note: Committee deferred menthol to the ongoing TPSAC consideration